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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/711,896	11/15/2000	Tohru Kayano	KAYANO 1	8185

7590 01/21/2004

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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/711,896	KAYANO ET AL.	
	Examin r	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-25* is/are pending in the application.

4a) Of the above claim(s) *10-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 10/27/03 in response to the non-final Office Action mailed 06/27/03.

Status of Claims

2) Claims 1, 5, 24 and 25 have been amended via the amendment filed 10/27/03. It is noted that claim 4 has been amended, yet is presented as '(Original)'.

Claims 3 and 26 have been canceled via the amendment filed 10/27/03.

Claims 1, 4-9, 24 and 26 are pending.

Claims 1, 4-9, 24 and 26 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the specification made in paragraph 6 of the Office Action mailed 06/27/03 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Moot

6) The rejection of claim 26 made in paragraph 9(b) of the Office Action mailed 06/27/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of cancellation of the claim.

7) The rejection of claims 2 and 3 made in paragraph 8 of the Office Action mailed 06/27/03 under 35 U.S.C § 101 as being directed to a non-statutory subject matter is moot in light of Applicants' cancellation of the claim.

8) The rejection of claim 3 made in paragraph 9(c) of the Office Action mailed 06/27/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

9) The rejection of claim 2 made in paragraph 9(d) of the Office Action mailed 06/27/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

10) The rejection of claims 2, 3 and 26 made in paragraph 9(e) of the Office Action mailed 06/27/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 2, 3 and 26 made in paragraph 11 of the Office Action mailed 06/27/03 under 35 U.S.C. § 102(b) as being anticipated by Sana *et al.* (WO 97/44468), is moot in light of Applicants' cancellation of the claims.

12) The rejection of claims 2, 3 and 26 made in paragraph 12 of the Office Action mailed 06/27/03 under 35 U.S.C. § 102(b) as being anticipated by Akita *et al.* (*J. Biol. Chem.* 272: 26595-26603, October 1997), is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

13) The rejection of claim 1 and those claims that depend from this claim made in paragraph 8 of the Office Action mailed 06/27/03 under 35 U.S.C § 101 as being directed to a non-statutory subject matter is withdrawn in light of Applicants' amendment to claim 1.

14) The rejection of claim 24 made in paragraph 9(a) of the Office Action mailed 06/27/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to claim.

15) The rejection of claim 1 made in paragraph 9(c) of the Office Action mailed 06/27/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to claim.

16) The rejection of claim 5 made in paragraph 9(e) of the Office Action mailed 06/27/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to claim.

17) The rejection of claim 4-9, 24 and 25 made in paragraph 9(e) of the Office Action mailed 06/27/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

18) The rejection of claims 1, 4-9, 24 and 25 made in paragraph 11 of the Office Action mailed

06/27/03 under 35 U.S.C. § 102(b) as being anticipated by Sana *et al.* (WO 97/44468), is withdrawn.

Rejection(s) Maintained

19) The rejection of claims 1, 4-6, 24 and 25 made in paragraph 12 of the Office Action mailed 06/27/03 under 35 U.S.C. § 102(b) as being anticipated by Akita *et al.* (*J. Biol. Chem.* 272: 26595-26603, October 1997), is maintained for reasons set forth therein and herebelow.

20) The rejection of claims 1 and 9 made in paragraph 14 of the Office Action mailed 06/27/03 under 35 U.S.C. § 103(a) as being unpatentable over Akita *et al.* (*J. Biol. Chem.* 272: 26595-26603, October 1997), is maintained for reasons set forth therein and herebelow.

Applicants contend that the antibody disclosed in Figure 6 of Akita *et al.* is prepared using mature IL-18 as an antigen. Applicants state that the antibody described in Akita's Figure 6 binds to both mature IL-18 and pro hIL-18 at the same level of intensity. Applicants allege that the density of the bands for mature IL-18 and pro hIL-18 shown in Figure 6 are almost the same. Applicants submit that the claimed antibody has a higher immunoreactivity to interleukin 18 precursor than to mature interleukin 18 by at least 10 times. With regard to the rejection made under 35 U.S.C. § 103, Applicants state that the antibody specific to interleukin 18 precursor of the present invention has great industrial usefulness as a method of distinguishing interleukin 18 precursor from mature IL-18 and that Akita provides no motive or incentive for assembling an immunoassay kit. With regard to the inclusion of claim 1 in the obviousness rejection, Applicants allege that it is clearly impossible for a claim to be both anticipated by a reference and obvious from that same reference.

Applicants' arguments have been carefully considered, but are non-persuasive. The claimed product is an isolated antibody 'specific to an interleukin 18 precursor' as recited, and Akita *et al.* taught such an antibody. The industrial usefulness of a product represents the intended use of that product and has no patentable weight. Whether or not the antibody was made using mature IL-18 or prohIL-18 is irrelevant. Even if the instant claims were presented as product-by-process claims, as clearly explained in paragraph 14 of the Office Action mailed 06/27/03, the product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Any prior art antibody that has the recited structure and/or specificity irrespective of the process by which the antibody was produced would anticipate the instantly

claimed antibody. Contrary to Applicants' assertion, Akita's Figure 6 does teach that the mAb 25-2G reacted with higher intensity with prohIL-18 (see the bottom Figure 6B panel, the middle column). The clearly visible more intense immunoreactivity of the prior art antibody with prohIL-18 as depicted in the bottom B panel of Figure 6 is viewed as being equivalent to at least ten times higher as compared with the immunoreactive intensity with mature hIL-18. Since the Patent Office does not have the facilities for examining and comparing Applicants' compound or product with that of the prior art, the burden is on Applicants to show that a difference exists between the claimed invention and that of the prior art. The burden is shifted to Applicants to show that the antibody product of the prior art does not possess the same structural and functional characteristics of the antibody of the instant invention. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977). It should further be noted that the claiming of a new function, a new use or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

With regard to the inclusion of claim 1 in the rejection made under 35 U.S.C. § 103, it should be noted that every limitation in a claim has to be met by the rejection made. Claim 9 includes the limitation 'claim 1' (see line 2 of claim 9), and therefore the scope of claim 1 is necessarily included in claim 9. Therefore, in order to cover the limitation, claim 1 was included in the rejection statement. Contrary to Applicants' assertion, "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. § 103 and for anticipation under 35 U.S.C. § 102". *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

New Rejection(s)

Applicants are asked to note the new rejection(s) made in this Office Action. Applicants' amendments necessitated the new ground(s) of rejection presented in this Office Action.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

21) Claims 1, 4-9, 24 and 25 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is indefinite in the recitation: 'antibody specific to an interleukin 18 precursor ..... which has higher immunoreactivity to said interleukin 18 precursor than to mature interleukin 18

by at least 10 times', because it is unclear how an antibody also reactive with a mature interleukin 18 can be called as an antibody 'specific' to interleukin 18 precursor. In fact, because of its reactivity with mature interleukin 18, this antibody becomes a 'non-specific' antibody.

(b) Claim 1 is vague and confusing in the recitation: 'determined on an enzyme immunoassay', as opposed to, --determined by an enzyme immunoassay--.

(c) Claim 4 is confusing and/or grammatically incorrect in the recitation: 'precursor is a primate or rodent origin' as opposed to --precursor is of a primate or rodent origin-- as was recited in the original claim 4.

(d) Claims 4-9, 24 and 25, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

22) Claim 1 and those that depend therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, is directed to an isolated antibody 'specific' to an interleukin 18 precursor 'which has a higher immunoreactivity to said interleukin 18 precursor than to mature interleukin 18 by at least 10 times when determined on an enzyme immunoassay'. Applicants point to pages 32-35, Example 2 and line 6 of page 34 to line 9 of page 35 of the specification as providing descriptive support for the limitations. However, a review of this part of the specification shows that there is no descriptive support for the now included limitations. The specification, as originally filed, especially at lines 6-8 of page 35 states as follows:

> Each antibody exhibited an immunoreactivity against human IL-18 only at about 10% to about 2:% or less of that against human IL-l8 precursor.

This conveys that a specific antibody showing 100% immunoreactivity against human IL-18 precursor exhibits 'about 10%' to about 2% 'less' immunoreactivity against 'human IL-18'. First, there is no mention of any 'mature' interleukin 18 here. Secondly, about 10% less reactivity with IL-18 compared to that with precursor IL-18 implies that the antibody's immunoreactivity with IL-18 is

90%. This is not the same as the antibody immunoreactivity that is 'at least 10 times' higher with IL-18 precursor. Furthermore, an antibody immunoreactive with mature interleukin 18 cannot be identified as an antibody 'specific' to an interleukin 18 precursor, because it is a non-specific or a cross-reactive antibody. Therefore, the new limitations in the instant claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C § 103

23) Claims 1, 4-8 and 24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yong *et al.* (*Immunological Journal* 15: 226-228, October 1999 - original and English translation) in view of Campbell AM (*In*: *Monoclonal Antibody Technology*. Elsevier Science Publishers, The Netherlands, Chapter 1, pages 1-32, 1984).

The page number referred to for Yong's reference represents the page number in the translated document.

Yong *et al.* taught a purified recombinant human interleukin-18 precursor expressed in *E. coli* via a recombinant plasmid, pQEIL 18p. Yong *et al.* identified a 36 amino acid-long amino terminal end of hIL-18 precursor protein to be an unusual leader sequence. This leader sequence of the prior art is structurally identical to the instantly recited SEQ ID NO: 1 (see entire document, especially pages 5, 6, 8, 10 and 11; and Figures 1 and 2).

Yong *et al.* do not teach an isolated antibody specific to the human interleukin-18 precursor or SEQ ID NO: 1 wherein the antibody is at least ten times more immunoreactive with the human interleukin-18 precursor than with mature interleukin 18.

However, methods of producing antibodies to a specific polypeptide were well known in the art at the time of the invention. Furthermore, Campbell taught that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make antibodies to it

sometimes without a clear objective for their application. Campbell also taught that protein macromolecules can be studied in the field of research using these antibodies (see page 29, last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to generate and isolate a monoclonal or polyclonal antibody or a hybridoma cell line to Yong's purified interleukin 18 precursor or the unusual leader sequence of SEQ ID NO: 1 using art-known antibody production or hybridoma techniques to produce the isolated antibody or hybridoma of the instant invention, with a reasonable expectation of success. It is implicit that the resultant antibody produced using the specific interleukin 18 precursor or its leader sequence as the immunogen would bind to the homologous interleukin 18 precursor or its leader sequence with higher (i.e., at least 10 times higher) immunoreactive intensity than to mature interleukin 18, which was not the immunogen used to raise the antibody. Given Campbell's teaching that antibodies to a protein are made in the art without a clear objective for their application, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of producing an antibody to Yong's protein in order to study the protein or the unusual leader sequence for research purposes as taught by Campbell.

Claims 1, 4-8 and 24 are *prima facie* obvious over the prior art of record.

24) Claims 9 and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yong *et al.* (*Immunological journal* 15: 226-228, October 1999 - original and English translation) as modified by Campbell AM (*In*: *Monoclonal Antibody Technology*. Elsevier Science Publishers, The Netherlands, Chapter 1, pages 1-32, 1984) as applied to claims 1 and 24 above.

The teachings of Yong *et al.* as modified by Campbell are described above, which do not teach an immunoassay kit comprising an antibody to interleukin 18 precursor as recited, or the antibody contained in a pharmaceutically acceptable carrier.

However, methods of assembling an immunoassay kit using an antibody product was well known and routinely practiced in the art, and would have been obvious to a skilled artisan at the time the invention was made to produce such a immunoassay kit for diagnostic purposes using the antibody of Yong *et al.* as modified by Campbell *et al.* One of skill in the art would have been motivated to produce the instant invention for the expected benefit of making readily available the

prior art antibody, or for commercializing the prior art antibody for diagnostic use, since it is routine and conventional to use antibody reagents in immunoassay kits.

Similarly, adding a pharmaceutically acceptable carrier to an antibody is routine and very conventionally practiced in the art. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add an art-known pharmaceutical carrier to the prior art antibody of Yong *et al.* as modified by Campbell *et al.* to produce the instant invention with a reasonable expectation of success, since it is quite conventional to have an antibody mixed with in a pharmaceutical carrier for diagnostic purposes.

Claims 9 and 25 are *prima facie* obvious over the prior art of record.

Remarks

25) Claims 1, 4-9, 24 and 26 stand rejected.

26) Applicants' amendments necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

27) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The TC 1600 facsimile center receives papers 24 hours a day and seven days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

28) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number until January 2004 is (703) 308-9347

and (571) 272-0854 beginning February 2004. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

January, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER